The Mesolimbic Dopaminergic System as a Target for Nicotine

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Nicotine exerts diverse psychopharmacological actions both in man and in laboratory animals. The complexity of nicotine's profile of action probably reflects, in part, the widespread distribution of nicotinic receptors in the mammalian brain. Despite the large number of brain nuclei which appear to express these receptors, one neuronal pathway has received particular attention from several researchers - the mesolimbic dopaminergic system. This work, originating from different laboratories and using different experimental approaches, will be reviewed. It appears that nicotine, like the psychomotor stimulants d-amphetamine and cocaine, activates this pathway, and this action may have important behavioural consequences.

Mesolimbic dopaminergic neurons, which have their cell bodies in the ventral tegmental area of the mesencephalon, project principally to the nucleus accumbens and olfactory tubercle. All three areas have moderate to high densities of high-affinity ^{3}H-nicotine binding sites, and selective removal of dopaminergic neurons with the neurotoxin 6-hydroxydopamine leads to a marked reduction in ^{3}H-nicotine binding at the level of the cell bodies/dendrites and in the terminal regions as well. In addition, experiments using in situ hybridization histochemistry and immunohistochemistry have detected mRNA species and immunoreactivity associated with nicotinic receptors within the ventral tegmental area.

Electrophysiological experiments have confirmed that mesolimbic dopaminergic cells express nicotinic receptors and are stimulated by direct or systemic administration of nicotine. In vitro experiments show that nicotine can also act directly on dopaminergic terminals to promote the release of this neurotransmitter in the nucleus accumbens. Nicotine also enhances dopamine release from mesolimbic terminal regions in freely-moving rats, but the principal site of action is as yet unclear. Another open question is whether nicotine can stimulate mesolimbic dopamine release when the drug is given by a chronic continuous infusion rather than by acute administration.

Acute administration of nicotine can stimulate locomotor activity in rats, and this effect is more readily seen after repeated prior exposure to the drug. The locomotor stimulant effect is central in origin and reflects a stimulation of receptors. Psychomotor stimulant drugs such as d-amphetamine and cocaine appear to increase locomotor activity by enhancing dopaminergic transmission in mesolimbic terminal areas. This possibility has been examined for nicotine. In rats previously given the drug on a daily basis, nicotine produced a dose-related and stereoselective locomotor stimulant effect which was accompanied by a parallel increase in dopamine utilization in mesolimbic terminal regions. Selective depletion of mesolimbic dopaminergic terminal fields abolished the locomotor stimulant effect, indicating that nicotine-induced locomotion is not only accompanied by, but is dependent upon, activation of the mesolimbic dopaminergic system.

In summary, one important action of nicotine in the brain appears to be an activation of mesolimbic dopaminergic neurons. This action may underlie, *inter alia*, the behavioural stimulant effects of the drug.

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